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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,402	09/17/2001	Julio Cesar Aguilar Rubido	976-11 PCT/US	3056

7590 08/13/2003

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EXAMINER	
FOLEY, SHANON A	
ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 08/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/857,402	AGUILAR RUBIDO ET AL.	
	Examiner	Art Unit	
	Shanon Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-18,21-27 and 38-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-18,21-27 and 38-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *20* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

In paper no. 21, applicant amended claims 15-18, 22-27, cancelled claims 11-14, 19, 20, 28-37 and added new claims 38-41. At the top of page 3 of the response, applicant states that claims 21 and 22 are also cancelled, but this appears to be a typo since applicant has included a copy of claims 21 and 22 in the claim listing. Claims 15-18, 21-27 and 38-41 are under consideration.

Request for Continued Examination

The request filed on 6/2/3 for a Request for Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/857,402 is acceptable and a RCE has been established. An action on the RCE follows.

A careful review of applicant's arguments, amendments to the claims, as well as the declaration of Julio César Aguilar Rubido have been fully considered and have been found persuasive to obviate the rejections of the final Office action of June 4, 2002. However, upon further considerations of the claims, new grounds of rejection are required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17, 25, 27 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine

the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "nucleocapsid" in claims 17 and 40 are presumably used in the claims to mean "VLP's or virus-like particles", while the accepted meaning is "VLP, capsid or L1 and L2" because papillomaviruses do not possess nucleocapsids, see the definition of nucleocapsid provided by Harrison et al. Virus Structure. *In* B.N. Fields et al. (ed.), Fields Virology, 3rd ed. Philadelphia: Lippencott-Raven Publishers; 1996: 60. The term is indefinite because the specification does not clearly redefine the term. This rejection also affects claims 25 and 27. In the interest of compact prosecution, the vaccine antigen of human papillomavirus (HPV) is interpreted to be an HPV VLP because this is what is used in the working examples.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claim:

Claim 24 states that the vaccine composition is suitable for use as a preventative vaccine against HCV infection.

The nature of the invention:

Currently, there are no known agents with efficacy required to prevent HCV infection. The art does not disclose an active agent or combination of active agents which is recognized as an HCV prevention. The prior art does not teach or fairly suggest a treatment modality wherein healthy subjects are administered an active

agent or agent(s) and there is evidence that none of the associated symptoms or disease state characteristics are ever manifested. The disclosure does not direct the skilled artisan to an art which satisfies the requirement for preventing HCV infection.

The state of the prior art

Lanford et al. (ILAR Journal. 2001; 42 (2): 117-26, abstract only), teaches that the only acceptable animal model currently available for study of HCV infections is the chimpanzee. Since the working examples are limited to experiments in mice, the skilled worker would not accept that an increase in antibody response in mice to hepatitis antigens would sufficiently indicate that the instant vaccine composition has ameliorative or prophylactic properties with respect to HCV.

Applicant asserts in the declaration that chimpanzees are not required to illustrate therapeutic immunization. However, the claim requires that the instant vaccine is suitable to prevent HCV infection, but the disclosure does not provide sufficient evidence indicating that the vaccine composition is sufficient for the purpose recited in the claim.

Parr (Canadian Journal of Gastroenterology. 2000; 14 Suppl B: 83B-88B, abstract only) is a post-filing date reference, which explicitly states that there is no preventative vaccine available for HCV. The disclosure does not provide any data that would indicate that the instant formulation would prevent HCV infection.

The level of one of ordinary skill:

While one skilled in the art would be able to treat HCV infection, it is beyond the skill of the artisan to prevent HCV infection.

The level of predictability in the art:

Since the art does not disclose any HCV preventive agents, the skilled artisan would not predict, in the absence of proof to the contrary, that the active agent(s) instantly claimed are efficacious in preventing HCV infection. The assertion that the instant formulation is suitable to prevent HCV infection necessarily requires evidence to support applicant's assertion. One of skill in the HCV art could not predict, from the evidence of record, that the active agents asserted to be useful, can indeed prevent HCV-associated disease and infection.

The amount of direction provided by the inventor:

There is no sufficient guidance provided in the form of administration profiles, combination ratios of the active agents or reference to the same in the prior art to provide the skilled artisan with sufficient guidance to prevent HCV infection. Prevention is seen to encompass administering the active agent to a baby or small child or healthy adult, and noting the fact that symptoms of the condition/disease never manifest themselves. The instant specification does not demonstrate any evidence of protection from HCV disease.

The existence of working examples:

There is no data in the examples that would indicate to the skilled artisan that mice developed an immune response sufficient to block infection of HCV because the mice were not challenged with any virus after administration of the vaccine.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The disclosure does not provide sufficient evidence to support applicant's claim of HCV prevention. Due to the lack of working examples demonstrating protective efficacy, the state of the art which clearly states that there is no preventative vaccine formulation for HCV, the lack of predictability of the skilled artisan to use the instant composition to prevent HCV, and the lack of guidance provided by the inventor for using the instant composition as a vaccine for HCV, it is determined that an undue quantity of experimentation would be required for the skilled artisan to make and use the invention to prevent HCV infection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 15, 16 and 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Tabor et al. (US 4,547,368) in light of Bowen et al. (Research in Virology. 1992; 143 (4): 269-78 abstract only).

Claim 15 is drawn to a vaccine formulation suitable for mucosal administration comprising a mixture of a first vaccine antigen, which is HBsAg and a second vaccine antigen, which is a viral nucleocapsid. Both of the antigens are present from 0.001mg to

1 mg. Claim 16 specifies that the viral nucleocasid is derived from hepatitis B. Claim 21 states that the vaccine formulation is suitable for nasal administration. Claims 22 and 23 state that the vaccine formulation is suitable for use as a therapeutic or preventative vaccine, respectively.

Tabor et al. anticipate a combination vaccine formulation comprising a mixture of 20 μg of HBsAg and 50 μg of hepatitis B nucleocapsid, HBcAg, see column 3, line 20 to column 4, line 1 and claims 2 and 3. Although Tabor et al. teach subcutaneous injection of the antigen mixture, Bowen et al. teach that injected and nasally administered subunit vaccines are both efficacious, see the abstract provided. Therefore, the combination vaccine of Tabor et al. anticipates a suitable formulation for nasal administration.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 17, 25, 27 and 38-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tabor et al. in light of Bowen et al. as applied to claims 15, 16 and 21-23 above, and further in view of Rose et al. (US 6,153,201) and Hauser et al. (US 5,972,346).

Claims 17, 25 and 27 state that the vaccine formulation comprises an antigen from HPV that prevents and treats papillomavirus infection. Claim 38 is drawn to a vaccine formulation suitable for mucosal administration comprising a mixture of HBsAg and a second and a third vaccine antigen, where each antigen is present from 0.001mg to 1mg.

Claim 39 states that the second vaccine antigen is a viral nucleocapsid and claim 40 states that the second antigen is an HPV VLP. Claim 41 requires that the third vaccine antigen is HBcAg.

Tabor et al. teach a combination vaccine formulation comprising a mixture of 20 μg of HBsAg and 50 μg of hepatitis B nucleocapsid, HBcAg, see column 3, line 20 to column 4, line 1 and claims 2 and 3. Although Tabor et al. teach subcutaneous injection of the antigen mixture, Bowen et al. teach that injected and nasally administered subunit vaccines are both efficacious, see the abstract provided. Therefore, the combination vaccine of Tabor et al. anticipates a suitable formulation for nasal administration. Tabor et al. do not teach HPV VLP.

Rose et al. teach a method of inducing an immune response against papillomavirus infection by orally administering papillomavirus VLPs. The formulations of Rose et al. are also administered intranasally. The formulation of Rose et al. treats and protects against papillomavirus infection. See claims 1-6 and column 8, lines 35-38.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the HBsAg and HBcAg antigens of Tabor et al. with the HPV VLP of Rose et al. simultaneously treat or prevent hepatitis B and papillomavirus infections, see column 3, lines 1-10 of Hauser et al. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of combining the HBV antigens of Tabor et al. with the HPV VLP antigen of Rose et al. because the vaccines of Tabor et al. and Rose et al. are suitable for nasal administration and because Hauser et al. teach that HBV vaccines are effective when combined with other multivalent vaccine formulations, see claim 6 of Hauser et al. Therefore, the invention as

a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Applicant argues on page 13 of the response that there is no suggestion in Rose et al. to combine HBsAg with the HPV VLP.

Applicant's argument has been fully considered, but is found to be unpersuasive. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, motivation to combine the HBsAg with another viral antigen is found in the teachings of Hauser et al. The combined teachings of Tabor et al. and Rose et al. teach every limitation in the claim and Hauser et al. teach motivation to combine HBsAg with another viral antigen with a reasonable expectation of success. Therefore, a prima facie obvious case is evident from the teachings in the prior art.

Claims 15, 18 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wands et al. (US 6,025,341).

Claim 18 is drawn to the vaccine formulation comprising a hepatitis C nucleocapsid. Claim 26 states that the vaccine formulation is suitable to treat HCV infection.

Wands et al. teach a nucleic acid coding for a fusion protein comprising HBsAg and HCV core proteins that is used to treat HCV infection, see claims 1-4, column 6, lines 22-57. Wands et al. also teach that the fusion composition is suitable for mucosal administration, see column 11, lines 42-54.

One of ordinary skill in the art at the time the invention was made would have been motivated to administer the nucleic acid fusion protein of Wands et al. as a protein composition to eliminate the step of using host cell machinery to generate the fusion protein that elicits an immune response. While Wands et al. do not set forth a specific example exemplifying simulateous administration of unfused HBsAg and HCV core antigens in a mixture, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Therefore, the invention as a whole would have been prima facie obvious, absent unexpected results to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley
August 10, 2003

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800/1600